REMARKS

Information Disclosure Statement

A Supplemental Information Disclosure Statement (IDS) was filed at the U.S. Patent and Trademark Office on June 14, 2004. For convenience, a copy of this IDS including Form PTO-1449 is enclosed herewith. Entry of this IDS is respectfully requested.

Interview Summary

The substance of the Interview on August 2, 2004 between Examiner DeBerry, Examiner Kemmerer, Dr. Carney and the undersigned is set forth in the Interview Summary provided to Applicants by Examiner DeBerry after the Interview. The Interview Summary is incorporated herein by reference.

Reference AW3, which was cited in the IDS filed at the Patent Office on June 14, 2004, was also discussed during the Interview. It was discussed that this reference, particularly the last sentence of the reference, does not anticipate or render the claimed invention obvious because this teaching is nothing more than an invitation for further experiment. It was also discussed that this reference does not render the claimed invention obvious because it was surprising and unexpected that TP508 alone, in the absence of an osteoconductive scaffold or matrix, would be effective in inducing bone formation at a site in need of bone growth and at which bone growth would not occur at said site if left untreated, such as at non-union fractures, segmental bone gaps and bone voids. Evidence of the surprising and unexpected result that TP508 alone, in the absence of an osteoconductive scaffold or matrix, can induce bone formation at a site in need of bone growth and at which bone growth would not occur at said site if left untreated is provided in the Rule 132 of Declaration of Dr. Darrell Carney filed concurrently herewith.

Specification Amendment

The specification has been amended to correct a typographical error, namely to replace "Try" with "Tyr". It is noted that "Try" is not an abbreviation for any amino acid.

The specification has also been amended at page 7, line 5, to include a sentence reciting that the Asp-Ala of a thrombin receptor binding domain having the sequence Arg-Gly-Asp-Ala

comprise the first two amino acids of the serine esterase conserved sequence. This amendment to the specification is fully supported in the application as filed on July 19, 2001, which incorporates by reference the entire contents of U.S. Patent Nos. 5,352,664 and 5,500,412 (see page 5, line 3). The added sentence is recited at column 18, lines 3-8 of the '664 patent and at column 16, lines 31-36 of the '412 patent.

No new matter is added with the amendments to the specification.

New Claim 66 and Claims Amendments

New Claim 66 is fully supported in the application as filed on July 19, 2001. Support can be found, for example, at page 3, lines 10-15; page 3, lines 19-26; page 5, line 3, which incorporates by reference the entire contents of U.S. Patent Nos. 5,352,664 and 5,500,412 (see, e.g., column 18, lines 3-8 of the '664 patent and column 16, lines 31-36 of the '412 patent); page 6, lines 5-11; and page 7, lines 3-5.

Independent Claims 1, 53 and 63 have been amended to more clearly recite that the NPAR agonist is administered in a method to stimulate bone growth at a site in need of bone growth and at which bone growth would not occur at said site if left untreated. This amendment of the claims is fully supported in the application as filed on July 19, 2001. Support can be found, for example, at page 3, lines 19-26; and page 4, lines 3-6.

Claim 1 has also been amended to recite that the NPAR agonist is a polypeptide of between 12 and 23 amino acids in length and is represented by the structural formula Arg-Gly-Asp-Ala-R, wherein R is a serine conserved sequence. This amendment of the claims is also fully supported in the application as filed on July 19, 2001. Support for this amendment can be found, for example, at page 5, line 3, which incorporates by reference the entire contents of U.S. Patent Nos. 5,352,664 and 5,500,412 (see, e.g., column 18, lines 3-8 of the '664 patent and column 16, lines 31-36 of the '412 patent); page 6, lines 5-11; and page 7, lines 3-5.

Claims 4, 45, 46, 48, 50 and 52 have been amended to depend from Claim 1. Claims 51, 53, 56 and 61-63 have also been amended to correct a typographical error, namely to replace "Try" with "Tyr".

No new matter is added by the claim amendments.

Rejection of Claims 1, 4 and 45-60 Under 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 1, 4 and 45-60 stand rejected under 35 U.S.C. § 112, first paragraph, because, in the Examiner's assessment, the specification does not provide enablement for the use of any agonist of the non-proteolytically activated thrombin receptor in the claimed methods of stimulating bone growth at a site in a subject in need of osteoinduction or bone graft. However, the Examiner acknowledges that the specification is enabling for the use of "an agonist of the non-proteolytically activated thrombin receptor wherein the agonist is a thrombin derivative comprising a polypeptide 23 amino acids in length and is represented by the following structure Arg-Gly-Asp-Ala-R wherein R is a serine esterase conserved sequence and wherein Asp-Ala of said structure comprise the first two amino acids of the serine esterase conserved sequence" or "an agonist comprising SEQ ID NO:5" or "an agonist comprising SEQ ID NO:6" (Paper No. 20040504, at page 3, line 19 to page 4, line 7). The Examiner also acknowledges that a polypeptide of 12 amino acids in length exhibited activity, albeit the activity was not as great as that for the polypeptide of 23 amino acids (Paper No. 20040504, at page 6, lines 6-10).

Applicants respectfully disagree with the instant rejection for the reasons of record. However, in an effort to advance prosecution in the subject application and without acquiescing to the Examiner's rejection or waiving the right to prosecute the full scope of the original claims in the future, independent Claim 1 has been amended to recite that the agonist is a thrombin peptide derivative comprising a polypeptide of between 12 and 23 amino acids in length and is represented by the following structure Arg-Gly-Asp-Ala-R wherein R is a serine esterase conserved sequence; and independent Claim 53 has been amended to recite that the peptide is 23 amino acids in length and comprises SEQ ID NO: 5. Claims 4, 45-46, 48, 50-52 and 57-60 are dependent on Claim 1 and thus, carry the limitations of Claim 1. Claims 54-56 are dependent on Claim 53 and thus, carry the limitations of Claim 53. Claims 47 and 49 have been cancelled without prejudice. As amended, Claims 1, 45-46, 48 and 50-60 are drawn to subject matter that the Examiner acknowledges to be enabled. It is noted that a peptide with a lesser activity relative to a peptide with a greater activity does not mean that the peptide with the lesser activity lacks activity.

Reconsideration and withdrawal of the instant rejection under 35 U.S.C. § 112, first paragraph, are respectfully requested.

Rejection of Claim 1, 4 and 45-60 Under 35 U.S.C. § 112, First Paragraph (Written Description)

Claims 1, 4 and 45-60 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that Applicants had possession of the claimed invention at the time the application was filed. In particular, the Examiner states that the specification "fails to provide written description for any thrombin peptide derivative, truncated fragments or physiologically functional equivalent thereof" (Paper No. 20040504, at page 7, lines 7-9). However, the Examiner acknowledges that the specification provides adequate written description for SEQ ID NO 5, SEQ ID NO: 6 and "a thrombin derivative comprising a polypeptide 23 amino acids in length and is represented by the following structure Arg-Gly-Asp-Ala-R wherein R is a serine esterase conserved sequence and wherein Asp-Ala of said structure comprises the first two amino acids of the serine esterase conserved sequence" (Paper No. 20040504, at page 7, lines 3-7).

Applicants respectfully disagree with the instant rejection for the reasons of record. However, in an effort to advance prosecution in the subject application and without acquiescing to the Examiner's rejection or waiving the right to prosecute the full scope of the original claims in the future, independent Claim 1 has been amended to recite that the agonist is a thrombin peptide derivative comprising a polypeptide of between 12 and 23 amino acids in length and is represented by the following structure Arg-Gly-Asp-Ala-R wherein R is a serine esterase conserved sequence; and independent Claim 53 has been amended to recite that the peptide is 23 amino acids in length and comprises SEQ ID NO: 5. Claims 4, 45-46, 48, 50-52 and 57-60 are dependent on Claim 1 and thus, carry the limitations of Claim 1. Claims 54-56 are dependent on Claim 53 and thus, carry the limitations of Claim 53. Claims 47 and 49 have been cancelled without prejudice. As amended, Claims 1, 4, 45-46, 48 and 50-60 are drawn to subject matter that the Examiner acknowledges to be adequately described in the specification, as well as subject matter that is clearly described in the specification. As Applicants pointed out in the Amendment filed January 2, 2004, specific examples of NPAR agonists are described in the subject application as well as in U.S. Patent No. 5,352,664 ('664) and U.S. Patent No. 5,500,412 ('412), which are incorporated by reference in the subject application. Such NPAR agonists include polypeptides of between 12 and 23 amino acids in length and are represented by the structure Arg-Gly-Asp-Ala-R, wherein R is a serine esterase conserved sequence.

Reconsideration and withdrawal of the instant rejection under 35 U.S.C. § 112, first paragraph, are respectfully requested.

Rejection of Claims 1, 4 45-53, 56 and 60 Under 35 U.S.C. § 102(b)

Claims 1, 4, 45-53, 56 and 60 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Simmons *et al.* (*Calcium Metabolism: Comparative Endocrinology*, International Satellite Symposium, 2nd, San Francisco, CA, November 30, 1998).

Applicants respectfully disagree that Claims 1, 4, 45-53, 56 and 60 are anticipated by the teachings of Simmons *et al.* for the reasons of record. However, in an effort to advance prosecution in the subject application and without acquiescing to the Examiner's rejection, independent Claims 1 and 53 have been amended to recite that the peptide is administered in a method to stimulate bone growth in a subject at a site in need of bone growth and at which bone growth would not occur at said site if left untreated. Claims 4, 45-46, 48 and 50-52 are dependent on Claim 1, and Claim 56 is dependent on Claim 53, and thus, carry this limitation. Claims 47 and 49 have been cancelled.

Simmons *et al.* teach that TP508 enhanced the mechanical strength and accelerated the progression of rat femoral fracture healing. Healing of this fracture (bone regeneration) was occurring prior to TP508 treatment, indicating that treatment (including bone grafting and osteoinduction) was not required for normal bone growth. Thus, Simmons *et al.* teach that TP508 enhanced the mechanical strength and accelerated the rate of *normal* fracture healing in a fracture that normally heals without treatment. Simmons *et al.* do not teach or suggest the use of TP508 for stimulating bone formation at a site in need of bone growth and at which bone growth would not occur if the site was left untreated. As such, Claims 1, 4, 45-46, 48, 50-53 and 56 are not anticipated by the Simmons *et al.* reference.

Reconsideration and withdrawal of this rejection of Claims 1, 4, 45-46, 48, 50-53 and 56 under 35 U.S.C. § 102(b) are respectively requested.

Rejection of Claims 4 and 57-59 Under 35 U.S.C. § 103(a)

Claims 4 and 57-59 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Simmons *et al.* in view of Schmitz (U.S. Patent No. 4,637,931). Applicants respectfully disagree that Claims 4 and 57-59 are unpatentable over the cited art for the reasons of record.

Claims 4 and 57-59, which are ultimately dependent on Claim 1, carry the limitation recited in Claim 1 that the NPAR agonist is administered in a method to stimulate bone growth in a subject at a site in need of bone growth and at which bone growth would not occur at said site if left untreated.

The cited references (Simmons *et al.*, Schmitz), alone or in combination, would not have suggested the claimed invention to one of ordinary skill in the art at the time the invention was made with a reasonable expectation of success. More specifically, the cited references, alone or in combination, would not have suggested, with reasonable expectation of success, the use of a NPAR agonist in a method of stimulating bone growth in a subject at a site in need of bone growth and at which bone growth would not occur at said site if left untreated. Simmons *et al.* teach that TP508 can be used in enhancing the mechanical strength and accelerating the rate of *normal* fracture healing in a fracture that normally heals without treatment. Schmitz teaches the use of a bone repair material consisting of decalcified freeze-dried bone and biodegradable biodegradable, biocompatible copolymer for improving and accelerating the healing of osseous tissue. Importantly, neither reference teaches or suggests that NPAR agonists, including TP508, can stimulate bone growth within a subject at a site in need of bone growth and at which bone growth would not occur if the site were left untreated. In fact, prior to Applicants' results described in the subject application, one of ordinary skill in the art would not have reasonably expected that NPAR agonists could be used successfully to stimulate bone formation at a site in need of bone growth and at which bone growth would not occur if the site was left untreated.

Reconsideration and withdrawal of the rejection Claims 4 and 57-59 under 35 U.S.C. § 103(a) are respectfully requested.

Rejection of Claims 63 and 64 Under 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 63 and 64 have been rejected under 35 U.S.C. § 112, first paragraph, for failing to comply to comply with the enablement requirement.

With regard to Claim 63, the Examiner states that Claim 63 encompasses a method of stimulating bone growth at "any site" where bone would not normally be found, including the heart, liver, lung, etc., but "[t]he specification fails to teach why such a treatment is desirable and what subjects are in need of such treatment". Paper No. 20040504, at page 13, lines 14-19.

Claim 63 has been amended to recite that the *C*-terminal amidated peptide comprising SEQ ID NO: 6 is administered in a method to stimulate bone growth in a subject at an ectopic site in need of bone growth and at which bone growth would not occur at said ectopic site if left untreated, thereby obviating this aspect of the instant rejection. A site "in need of bone growth" clearly does not include heart, liver, lung, etc.

With regard to Claim 64, the Examiner states that the specification fails to provide guidance and working examples for the use of the *C*-terminal amidated peptide comprising SEQ ID NO: 6 in dental/periodental reconstruction, and, as such, it would require undue experimentation to show a correlation between the *C*-terminal amidated peptide comprising SEQ ID NO: 6 and dental/periodontal reconstruction given the teachings of Sigurdsson *et al.* (*J. Periodontol.*, 66(6):511-521 (1995)). Applicants respectfully disagree with the instant rejection. However, in an effort to advance prosecution in the subject application and without acquiescing to the Examiner's rejection or waiving the right to prosecute the full scope of the original claims in the future, Claim 64 has been cancelled.

Rejection of Claim 61 and 65 Under 35 U.S.C. § 112, Second Paragraph

Claims 61 and 65 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. In particular, the Examiner states that Claims 61 and 65 appear to be drawn to the same method.

Claim 65 has been cancel, thereby obviating this rejection.

Terminal Disclaimer

Transmitted concurrently herewith is a Terminal Disclaimer in which the owner of the instant application disclaims, except as provided in the Terminal Disclaimer, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond

the expiration date of the full statutory term of any patent on the pending second Application Number 10/050,692 filed on January 16, 2002.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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